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THE EFFICACY OF DEXTROAMPHETAMINE AS A MOTION SICKNESS COUNTERMEASURE FOR USE IN MILITARY OPERATIONAL ENVIRONMENTS

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Executive Summary

Motion sickness often leads to decrements in operational performance for personnel working in dynamic environments. Previous research examining pharmacological solutions for motion sickness have reported that dextroamphetamine (d-amphetamine) imparts significant protection against provocative motion, when compared to other standard countermeasures such as antihistamines, without conferring drowsiness or significant side effects. The military currently prescribes Dexedrine® to assist with fatigue deterrence during periods of high operational tempo and/or extended flight operations. If the reported anti-motion sicknesses properties of d-amphetamine can be confirmed, the military could utilize a single medication for motion sickness and fatigue prevention. The purpose of this study was to determine the efficacy and side effect profile of this potential motion sickness countermeasure for use in military environments. It was hypothesized that subjects in the oral d-amphetamine (10 mg, d-amphet) condition will tolerate more head movements than subjects in the placebo condition, without exhibiting performance decrements or significant side effects. Thirty-six aviation candidates, 31 male and 5 female, were recruited and randomized to one of two treatment groups (10 mg, d-amphet or placebo) and then exposed to passive Coriolis cross-coupling. Medication efficacy was determined by number of head movements tolerated between groups. Cognitive and medication side-effect profiles for both groups were derived from performance on the ANAM® Readiness Evaluation System (ARES®) cognitive battery, measurements of near-focus visual accommodation (VA), scores on the Karolinska Sleepiness Scale (KSS), and motion sickness questionnaires. Analyses failed to discern significant differences in the number of head movements tolerated between groups or treatment effects over time on the ARES® cognitive battery, VA, or KSS, $p > 0.05$. A negative linear relationship was found between Motion Sickness Susceptibility Questionnaire-Short (MSSQ- Short) scores and number of head movements ($r = -.24$, $p < .05$). In summary, d-amphetamine did not provide significant motion sickness protection when compared to placebo and no significant impacts on performance or medication-induced side effects were observed.

Introduction

Definition and History

Motion sickness is the body's normal physiological response to unrecognized movement elicited by various forms of real or apparent motion. The primary signs and symptoms are nausea, vomiting, drowsiness, pallor, increased salivation, flushing/warmth, cold sweating, headache, and dizziness. The earliest writings on motion sickness and its ill effects were recorded by the ancient Greeks whose word "naus", from which the word nausea originated, means ship. Seafaring militaries have been afflicted by the detrimental effects of motion sickness for as long as countries have set out to explore and conquer other lands. In the reviews by Bard (1948), Chinn & Smith (1955), Reason and Brand (1975), and Tyler & Bard (1949), several references are made to seasickness by ancient mariners and naval seamen, and land-based motion sickness by armies traveling by camel across the desert. Some investigation into the physiological causes and symptomological treatment of motion sickness were made during the 17th and 18th century, but the maladies of motion sickness afflicted a small segment of the population, and therefore motion sickness research did not receive significant scientific or public attention.

Early Motion Sickness Theories and Treatments

The late 19th and early 20th centuries saw a significant increase in travel via passenger ship, especially among the elite, and subsequently a heightened interest in the cause and alleviation of motion sickness. In an effort to relieve passenger ills, physicians and researchers attempted a wide range of sometimes bizarre remedies such as, narcotics, sedatives (including chloroform), alcohol, abdominal belts to restrict visceral mobility, strange food recommendations (pickled onions and champagne), atropine eye drops and dark glasses to prevent eye irritation, and psychological treatments for those who suffered from "mentally-induced" motion sickness. Most of these proposed remedies failed to provide acceptable relief and investigations into the potential cause and symptom-related treatment continued (Chinn & Smith, 1955).

In 1881, Irwin and de Champeaux (as cited in Reason & Brand, 1975) were the first to independently publish papers relating the symptoms of motion sickness to Meniére's disease and identifying the potential role of the vestibular system in the etiology of motion sickness. These theories were later confirmed in studies using individuals with compromised vestibular systems, with all investigators drawing similar conclusions; that a functioning vestibular system was necessary for the production of motion sickness symptoms (Minor, 1896; Pollack, 1893 & Reynolds, 1884). The confirmation of this new theory led to more physiological-based research and eventually identified the role of the central and autonomic nervous systems.

Although the physiological understanding of motion sickness remained rudimentary in the early 1900's, improved treatments were necessary for the comfort and health of the masses traveling by sea for weeks at a time. Hill (1937) reported symptoms of seasickness on passenger ships to be characterized by the same constellation of symptoms reported by early sea travelers; nausea, vomiting, drowsiness, apathy, headache, and vertigo. Although the etiology of

seasickness was not well understood, the collection of symptoms led him, and other medical professionals, to believe the symptoms were caused by a disruption in the balance between the sympathetic and parasympathetic nervous systems, and that in the nauseated state, the parasympathetic system had dominance (Keevil, 1938). With these physiologic assumptions in mind, early investigators determined they had two courses of action to remedy the problem; they could either directly decrease parasympathetic control or increase sympathetic tone, and thereby, activate parasympathetic inhibition.

Historical Use of Stimulants to Combat Motion Sickness

During the early part of the 20th century, the available pharmacological modulators of parasympathetic control were atropine and scopolamine. Hill (1937) used atropine, in conjunction with ephedrine, and reported some usefulness for motion sickness prophylaxis but the level of effectiveness did not warrant wide spread use. Hill also tested ephedrine alone and did not find any significant relief of symptoms. Keevil (1938) stated that belladonna (scopolamine) had been effective in treating seasickness among shipboard passengers; however, the side effects experienced were deemed to outweigh the benefits. Even with a change in the belladonna alkaloid administered, the depressive effect, mental confusion, and memory impairment of scopolamine were not alleviated and scopolamine was not considered a drug of choice (Keevil). The strategy for motion sickness relief then turned to pharmaceutical countermeasures that increase sympathetic tone. Myerson & Ritvo (1936) reported that Benzedrine had anti-spasmodic action on the gastrointestinal tract, specifically by decreasing hypertonicity of the stomach without negatively affecting normal peristalsis. In two separate case studies using Benzedrine, Keevil reported that subjects felt the effects of the medication in minutes and obtained significant relief from motion sickness symptoms. Although Benzedrine had a favorable outcome in this non-experimental trial, the author warned of the dangers of using this powerful stimulant in view of the potential for abuse, significant cardiovascular risk, and lack of effectiveness if the motion sickness stemmed from non-physiological causes.

Military Research Using Sympathomimetics for Motion Sickness

The military importance of motion sickness research did not become evident until after the turn of the 20th century. Troop transport by ship and plane made apparent the significant impact that motion sickness could have on personnel and their missions (Money, 1970; Reason & Brand, 1975). According to Chinn (1951, 1955), and Money (1970), the incidence of seasickness can range from 1% to 100% depending on the type of vessel and the sea conditions, and during a typical Atlantic crossing, 25-30% of crew become sick to the point of vomiting during the first two to three days. Also, studies considering the incident rate of airsickness in military training stated that 10-18% of student pilots experience motion sickness at some time during early training flights and some individuals never overcome the symptoms (Hemingway, 1946; Powell, Beach, Smiley & Russell, 1962; Tucker & Russell, 1966). This new operational problem prompted military researchers to forgo more in depth research on physiological causes and focus their attention on the efficacy of possible countermeasures.

Wood, Graybiel, McDonough, and Kennedy (1965) tested the effectiveness of seven potential anti-motion sickness medications, (plus two in combination), that included hyoscine

(the U.K. term for scopolamine), meclizine, and d-amphetamine. The purpose of the study was to standardize testing methods to allow a more exact comparison of the effectiveness of anti-motion sickness drugs. Efficacy results showed that hyoscine, d-amphetamine, meclizine, and hyoscine + d-amphetamine improved tolerance to a provocative motion by 147%, 70%, 50%, and 194% respectively. The researchers stated the most surprising result was the effectiveness of d-amphetamine over meclizine (bonamine), at the time considered second in effectiveness only to hyoscine. The researchers attributed d-amphetamine's apparent effectiveness to its action on the sympathetic nervous system. If motion sickness is caused by an imbalance in the autonomic nervous system, as very early investigators had theorized (Blackham, 1939; Hill, 1936; Keevil, 1938), then stimulation of sympathetic action, or blocking acetylcholine in the parasympathetic system, could place the system in balance and prevent the symptoms of motion sickness.

In two subsequent studies using the same stimulus and methodology, Wood, Graybiel, and Kennedy (1966) and Wood & Graybiel (1968) had the objectives of confirming the appropriateness of the stimulus and experimenting with dosage levels to better determine the effectiveness of the medications. In the first experiment (i.e., Wood, Graybiel & Kennedy, 1966), the same medications from the 1965 study were used, however, the dose of each medication was increased in order to investigate whether the previously achieved effectiveness could be enhanced. When the results from the two studies were compared, the therapeutic effect increased in two conditions, the single dose of 20 mg of d-amphetamine when compared to the 10 mg dose and the combination of d-amphetamine (20 mg) + hyoscine (1.2 mg) versus the 10 mg d-amphetamine + 0.6 hyoscine combination. Hyoscine + d-amphetamine tested in this study increased the head movements tolerated by 375% over placebo and the 20 mg dose of d-amphetamine improved tolerance by 170% over placebo. The single most effective drug in this study was hyoscine (0.6 mg), similar to the first study, but doubling the dose to 1.2 mg failed to improve efficacy. Moreover, the increased dose of hyoscine produced a significant increase in reported drowsiness, blurring of vision, fatigue, and nervousness. Subjects in the 1.2 mg hyoscine + 20 mg d-amphetamine condition reported less drowsiness than with hyoscine alone, but these subjects reported the largest number of incidences of vertigo and stomach awareness.

The second study (i.e., Wood & Graybiel, 1968) compared 16 anti-motion sickness medications, with eight variations in dosage and three different drug combinations (equaling 28 conditions), and again reported that hyoscine + d-amphetamine was highly effective and that d-amphetamine alone offered more protection than the antihistamines meclizine and cinnerizine. The experimenters stated that the efficacy of d-amphetamine alone was a chance finding as the drug was being given in combination with hyoscine to counter drowsiness and was only given alone for the purposes of experimental control. Even so, when medications were rank-ordered by effectiveness, the 10 mg d-amphetamine condition ranked in the middle of the antihistamine group and gave better protection than 17 other treatment conditions. In addition, subjects in the 10 mg d-amphetamine condition did not report an increase in medication-induced side effects, often associated with anti-motion sickness medications. Other investigations into the side-effect profile of d-amphetamine reported similar results. Kennedy, Odenheimer, Baltzley, Dunlap and Wood (1990) and Schmedtje, Oman, Letz and Baker (1988), examined the potential cognitive effects of d-amphetamine and reported no performance decrements on cognitive tasks such as digit substitution, simple reaction time, digit span memory, and pattern memory, while subjects showed an increase in manual dexterity and improved speed related to short-term memory.

These studies appear to reinforce the findings of Wood et al., (1966) and Wood & Graybiel (1968) that d-amphetamine appears to decrease the subjective feelings of drowsiness. Despite these results, scopolamine (0.6 mg) continued to be reported as the most effective single treatment for motion sickness owing to parasympatholytic action.

With the exception of the three aforementioned experiments, an extensive review of the literature did not reveal any other research utilizing amphetamine alone as a motion sickness countermeasure. Ephedrine is the only other stimulant with any significant history of testing for motion sickness symptom relief. In addition to the investigations of the 1930's and 40's, Wood et al., (1966), Wood & Graybiel (1968), and Tokolo et al., (1984) tested ephedrine, and ephedrine in combination with scopolamine, and a variety of other anti-motion sickness medications, however, the results from these studies were mixed.

The Use of Sympathomimetics in Space

During the 1960's and 70's, National Aeronautics and Space Administration (NASA) scientists learned that astronauts experienced Space Adaptation Syndrome, a type of motion sickness induced by lack of normal gravitational forces. The first therapeutic regimen used for Space Adaptation Syndrome was 0.3 mg scopolamine + 5 mg d-amphetamine administered during the Skylab missions (Graybiel, 1980). The addition of a sympathomimetic was required to counter the sedative effects of scopolamine, and was also necessary later when promethazine became the standard protocol (Homick, 1979). Motion sickness researchers at NASA found d-amphetamine was successful in alleviating the sedating effects of anticholinergic and antihistaminergic drugs and synergistically aided in relieving the symptoms of motion sickness. However; based on the research by Wood et al., (1966), and Wood & Graybiel (1968), and the documented impairment anticholinergics have on psychomotor and cognitive performance, an examination of the apparent synergistic effect of sympathomimetics with anticholinergics was deemed necessary to determine if sympathomimetic drugs were the more effective anti-motion therapy (Kohl, Dick, Calkins & Mandell, 1986). Kohl and colleagues tested methamphetamine, phenmetrazine, phentermine, methylphenidate, and pemoline prior to exposure to controlled Coriolis cross-coupled accelerative stimulation and reported that all of the substances demonstrated significant therapeutic effects in delaying the onset of motion sickness. In addition, two of the drugs rendered lower incidences of side effects compared to the other treatments. This NASA research team suggested that sympathomimetic drug action may be acting directly on anti-motion sickness mechanisms by stimulating transmission at dopaminergic, noradrenergic and epinephrinergic synapses and that anticholinergic and antihistaminergic agents may indirectly correct the autonomic nervous system imbalance by blocking neurotransmission at cholinergic and histaminergic synapses. The conclusion from this study was that motion sickness research should shift from an emphasis on performance-detrimental agents, such as scopolamine and promethazine, to new alternative drugs within the sympathomimetic drug class.

Use of Stimulants in Military Aviation

Motion sickness is not the only human performance factor that negatively impacts operational missions. Fatigue has become a major concern of the aviation community with the increase in operational commitments world wide and decrease in manning levels over the past 15

years. Due to d-amphetamine's stimulation of the central nervous system (CNS), and its ability to improve alertness and postpone the need for sleep, the U.S. military selected Dexedrine® (d-amphetamine) as a fatigue countermeasure for use in aviation operations (Emonson & Vanderbeek, 1995). Researchers have tested non-pharmaceutical options such as, exercise prior to missions, strategic naps, cold air, noise, and controlled work schedules, all with only modest impacts on fatigue and operational effectiveness (Angus and Heslegrave, 1985; Angus, Pigeau & Heslegrave, 1992; LeDuc, Caldwell, Ruyak, Prazinko, & Gardner, 1998). Pharmacological countermeasures have proven more effective in maintaining performance of fatigued individuals engaged in tasks that are sedentary in nature, like piloting an aircraft, where the consequences of attention deficits and judgment errors can be deadly (Caldwell, Smythe, LeDuc & Caldwell, 2000). Although a variety of stimulants have been tested for use in high-tempo operational settings to combat fatigue, to date, d-amphetamine is the only stimulant on the "cleared to fly" list for aviators (Ambrose et al., 2001). Not only does amphetamine reduce excessive sleepiness, but Caldwell et al., found that flight performance, physiological arousal, and mood were sustained by Dexedrine® during 64 hours of continuous wakefulness. With early research indicating amphetamine's potential as a motion sickness countermeasure, and the current use of d-amphetamine as a fatigue deterrent, further testing is warranted to determine if the military could resolve motion sickness and fatigue with a single treatment.

Objectives and Hypotheses

The objective of this study was to investigate previous findings that d-amphetamine possesses anti-motion sickness properties without negative impacts on cognitive performance and subjective measurements of alertness. It is hypothesized that subjects in the dextroamphetamine condition will tolerate a significantly greater number of head movements during exposure to a provocative stimulus than subjects in the placebo condition and that performance on cognitive tests, visual accommodation, and side effect questionnaires will not be degraded with the use of dextroamphetamine when compared to placebo.

Method

Subjects and Motion Stimulus

Subjects. Thirty-six aviation candidates (31 males and 5 females) with an age range of 21-31 years (mean = 23.6 yrs, *SD* = 2.4) voluntarily participated in this study. All participants had a current flight physical and were medically screened for vestibular, gastrointestinal, neurological, and hepatic abnormalities, or any other health issue that would make them ineligible for a Food and Drug Administration clinical drug trial or motion study. In addition, volunteers were asked to refrain from taking prescription or over the counter medications, using tobacco products and drinking alcoholic beverages while engaged in the study. Descriptive statistics for the groups are summarized in Table 1. The protocol was approved by the Naval Aerospace Medical Research Laboratory (NAMRL) Institutional Review Board (IRB). Each subject provided written informed consent before participating in the study.

Stimulus. The Human Disorientation Device (HDD; Appendix 1) provided passive, Coriolis cross-coupling stimulation by rotating the subject about the earth's vertical and

horizontal axes in combination (Hixon & Niven, 1969). Subjects sat in a chair, which was located inside a metal sphere, and were restrained with an aviator-style 4-point seat belt and a padded head fixture to prevent extraneous movement and to ensure head-centered movement during rotation. The subject's gaze was directed to a black visual field inside the device to provide a standard, easily reproducible visual stimulus. The staircase profile of counter-clockwise rotation about the vertical axis began with a velocity of 1 rpm and increased in increments of 1 rpm/min, while rotation about the horizontal axis consisted of a 40-degree roll to the right, back to center, then left in a 3 second/direction sequence for a maximum of 40 minutes. The motion sickness endpoint for test termination was a self-report of moderate nausea that persisted for one minute or a maximum rotational speed of 40 rpm.

Experimental Procedures

Recruitment. A total of 167 aviation candidates were medically screened (145 male, 22 female), of which, 72 were accepted into the study and randomized to one of four treatment conditions (10 mg oral D-amphet, 0.4 mg intranasal scopolamine, 0.8 mg oral scopolamine, or placebo). Due to the fundamental differences between d-amphet and scopolamine, the only groups discussed in this report are the 10 mg oral D-amphet and placebo groups. Evaluations of the intranasal and oral scopolamine groups compared to the same placebo group were released in a separate report. Subjects cleared for participation were scheduled for two laboratory visits, one visit for practice on the ANAM® Readiness Evaluation System (ARES®) cognitive battery and the Visual Accommodation test (VA; Neely, 1965: Appendix 2), and one visit for motion sickness testing.

Practice day. A practice session for the ARES® cognitive battery and VA test was conducted to ensure performance asymptote was reached prior to actual data collection. The practice session (Appendix 3) consisted of six blocks of the ARES® administered on a Palm® Personal Digital Assistant (PDA; Tungsten E Model). VA testing consisted of 4 trials using the Royal Air Force (RAF) Rule. Each subject's test day was scheduled to ensure that no more than 2 days elapsed between the practice session and the test day. In addition, to offset any performance decay, a warm-up session of 2 blocks of ARES and 2 VA tests were conducted prior to establishing baseline scores on test day.

Test day. Subjects reported to the lab at 7:15 am, were given a compliance questionnaire to ensure adherence to testing restrictions and if applicable, were also given a urine pregnancy test. Once cleared for participation, baseline scores on the ARES® cognitive battery, VA, and Karolinska Sleepiness Scale (KSS) were established (Akerstedt & Gilberg, 1990; Timeline: Appendix 4). Subjects were given either oral D-amphet or oral placebo at 8:00 a.m. at the conclusion of baseline testing in a double blind fashion. Subject rotation began 75 minutes post-dose and continued until moderate nausea was reported for one minute unabated or a maximum speed of 40 rpm was obtained. Data collection on cognitive and performance side-effects (i.e., ARES®, VA, and KSS) were taken five times post-dose over three hours. The duration of the ride and number of head tilts tolerated were recorded and used to determine treatment efficacy. Subjects were discharged at 3.5 hours post-dose or when all medication or motion symptoms had returned to baseline.

Motion Sickness Ratings

The motion sickness symptom report, modified from the Pensacola Motion Sickness Questionnaire (MSQ; Hutchins & Kennedy, 1965) was used to guide the subject's self-report of common motion sickness symptoms including: nausea, dizziness, cold sweating, increased salivation, warmth/flushing, drowsiness, and headache for each minute of motion exposure. Subjects were asked to rate experienced symptoms as minimal, moderate, or major based on pre-established definitions. Stomach awareness and stomach discomfort were reported as present or not present. One pre-rotation symptom assessment was conducted to determine any pre-existing symptoms. Symptoms were then collected at the end of each minute just prior to advancement to the next increase in rpm. One post-rotation assessment was completed prior to the subject exiting the motion device to assess recovery.

Efficacy

Efficacy was determined by the average number of head tilts tolerated per group. Each minute of stimulation was equal to 12 head tilts. According to Miller and Graybiel (1970), performing standard head movements (+/-90° in the frontal and sagittal planes) while seated in a rotating chair kept at a constant rotational velocity produces symptoms of motion sickness in approximately 90% of subjects, usually within 20 minutes. The stimulus profile was computer controlled by Labview® (National Instruments Corporation, Austin, TX) software, as was the collection of the total number of head tilts and ride duration.

Questionnaires

Motion Sickness Susceptibility Questionnaire Short-form (MSSQ-Short). The MSSQ-Short was designed to determine how susceptible an individual is to motion sickness and what kinds of motion stimuli were most associated with motion sickness during childhood and over the past 10 years (Golding, 2003; 2006). Sickness was defined as feeling queasy, nauseated, or actually vomiting after exposure to a variety of motion stimuli involving land, sea, and air travel, as well as funfair (amusement) rides. Although not used as a study inclusion criterion, the MSSQ-Short provided a statistically valid means to ensure the groups were equally balanced and representative of the normal population regarding motion susceptibility. The MSSQ-Short has an internal reliability of 0.87 (Golding, 2006).

Karolinska Sleepiness Score. The KSS measures sleepiness using a nine point scale based on five states, ranging from "extremely alert" to "extremely sleepy, fighting sleep". There are four intermediary states that are not designated with words. Previous research has found that the KSS is closely linked to the objective measures of encephalographic and oculographic signs of sleep onset (Akerstedt & Gilberg, 1990). Scores on the KSS were used to determine the potential impact of medication on alertness.

Cognitive Tests

A Palm® Pilot PDA was used to administer the ARES®, a customized, Tri-Service Test Battery of objective cognitive tests consisting of: Simple Reaction Time, Running Memory, Logical Reasoning, and Matching to Sample (Elsmore & Reeves, 2004). Further information regarding ANAM® and ARES® cognitive batteries may be found in Reeves, Winter, Bleiberg and Kane's ANAM® historical perspectives article (2007). These particular cognitive tests were chosen because they are sensitive to medication-induced performance effects (Appendix 5); (Elsmore, Reeves & Reeves, 2007; Kane, Roebuck-Spencer, Short, Kabat & Wilken, 2007; Lewandowski, Dietz, & Reeves, 1995).

Visual acuity assessment

The RAF rule (Neely, 1956) was used to measure visual accommodation (near-focus). Subjects held one end of the rule just under the eyes and looked down the rule at a box, which was mounted on a slide, located at the opposite end. Subjects were instructed to read a line of text printed on the face of the box repeatedly while the box was slowly advanced toward them. Subjects were instructed to say "stop" when the text became blurred. The number (in cm) corresponding to the box location on the rule was recorded as the VA score. The VA test was given to detect potential changes in foveal vision.

Physiologic Monitoring

The Welch Allyn Propaq Encore® (Model 206 EL) was used to measure blood pressure and heart rate and Welch Allyn's Sure Temp Plus® was used to determine the subject's temperature. This information was collected for safety and to provide additional information regarding potential medication effects.

Statistical Analyses

SPSS version 12.0 for Windows® (SPSS Inc., Chicago, IL) was used for statistical analyses. The alpha level was set at 0.05 for all hypothesis tests. Data that qualified for ANOVA were assessed for homogeneity and normality. A Pearson correlation coefficient was calculated to establish the relationship between total head movements tolerated and scores on the MSSQ-Short. An ANCOVA, using the MSSQ-Short scores as a covariate, was calculated to compare mean number of head movements tolerated between groups to control for motion sickness susceptibility. A series of two-factor ANOVAs were conducted on data from the KSS, VA, and the ARES® cognitive battery to examine the side-effect profiles of each treatment condition. Specific components of the ARES® cognitive battery used in the side-effect analysis included: Simple Reaction Time, Running Memory, Logical Reasoning, and Matching to Sample. Physiological data were analyzed using an ANOVA to test for drug-by-time interactions.

Results

A significant correlation was found between the MSSQ-Short and the total number of head movements (r = -.24, $p < 0.05$), therefore, scores from the MSSQ-Short were used as a covariate in the primary analysis to control for individual variability in motion sickness susceptibility. The ANCOVA revealed no significant differences in the mean number of head movements tolerated between groups, F (1, 33) = .011, $p > 0.05$. The estimated marginal means for head movements tolerated by group is depicted in Figure 1 and Table 2. Results of repeated measures ANOVAs found no significant performance differences for treatment groups over time for either visual accommodation or the KSS (Figs. 2 & 3 and Table 3). Likewise, no significant drug-by-time interactions were detected regarding performance on the four ARES cognitive tasks (Simple Reaction Time, Running Memory, Logical Reasoning, and Matching to Sample) (Figs. 4 & 5 and Table 4). The ANOVA comparing systolic blood pressure for the two groups revealed no significant drug-by-time interaction, $p > 0.05$, (Fig 6). Baseline systolic blood pressure values in the D-amphet group started at a higher level than the placebo group and remained higher throughout the experiment, with the exception of one time point where the values were equal. There was no difference in baseline diastolic blood pressure values between the two groups and no significant difference over the five time points post-dose. Also, no significant post-rotation decrease in either diastolic or systolic blood pressures was experienced by the D-amphet or placebo group. Analysis of heart rate data resulted in a significant drug-by-time interaction with heart rates in the D-amphet group remaining higher than those in the placebo group, F (5, 170) = 3.56, $p < 0.05$ (Fig. 7).

Discussion

The results from the analysis of head movement data revealed that the experiment did not achieve the necessary power to make clear inferences regarding efficacy (power = .27, partial eta squared = .074). The large variance in the head movement data for the two groups (D-amphet, 214 ± S.E. 28.13 and placebo, 210 ± S.E. 28.13) demonstrates the extreme individual difference in motion sickness susceptibility, and therefore, tolerance to a sickening stimulus. To determine if motion sickness susceptibility affected the outcome, the average MSSQ scores for the groups were examined and no significant difference was found between the two groups (D-amphet = 4.6 and Placebo = 3.6). Even when using MSSQ scores during statistical analyses to control for individual susceptibility, no differences were detected in head movements tolerated. In contrast to the current study, reports by Wood et al., (1965; 1966) and Wood and Graybiel (1968) found significant individual differences in the tolerance to motion, prompting the researchers to use a repeated measures design which allowed each subject to act as their own control, and in two of the studies, subjects who were deemed highly resistant were excluded. Perhaps the use of a cross-over design, and screening for susceptibility, would have better controlled the individual variance inherent in motion sickness work. Without sufficient power in the analysis, a conclusion regarding efficacy can not be clearly made, however, the small effect size would cause one to surmise that increasing the number of subjects to achieve adequate power would not have resulted in a significant outcome.

Another methodological factor to consider when determining medication efficacy is the time of drug administration in relation to time of rotation. The timing of drug administration in

this study was similar to the previous study conducted by Wood et al., (1966) and was planned to coincide with the time of maximum drug concentration for d-amphetamine. Although plasma assays confirming d-amphetamine absorption were not performed, the 75 minute – 115 min post-dose to post-rotation should have allowed adequate time to reach systemic therapeutic levels (T_{max} = 90 min). Therefore, the lack of efficacy found for the d-amphetamine condition is probably not the result of inadequate medication absorption.

One unexpected result found in this study was the lack of significant cognitive performance changes and side effects in the D-amphet group. The literature is replete with studies testing the effects of d-amphetamine on motor and cognitive performance with most revealing similar performance changes such as faster times on tasks requiring speed (reaction time), slower times on more complex tasks, with the changes being dose dependent. Kennedy et al., (1990) examined differential performance effects of d-amphetamine (10 mg) on a series of nine computer-based tests and found enhanced (faster) scores on tapping tasks and a speed-related Short Term Memory (Sternberg) task, but subjects performed significantly worse on the more complex task, Pattern Comparison. Another study by Wesensten, Killgore, and Balkin (2005) examining the effects of d-amphetamine (20 mg) on executive function reported that d-amphetamine had a detrimental effect on the Stroop task. The present study used cognitive tests with reaction time components, and also more complex tests which measure conceptual processing and efficiency, all of which are typically useful for detecting medication-related changes. The analysis conducted on the four ARES® cognitive tests did not show any significant improvement in reaction time on simple tasks or decrement in mental processing speed on more complex tasks. The only difference in the approach to cognitive testing used during this trial compared with previous studies was administration of tests on a Palm® Pilot compared to the traditional Personal Computer (PC). Validation testing was conducted by this lab (McGrath, Lawson & Kass, 2007) prior to using the Palm® Pilot for test administration and the results confirmed that the shared tests were reliable and stable regardless of platform. In addition, Elsmore et al., (2007) confirmed the validity and reliability of using a small handheld device for execution of the ARES battery.

The lack of significant findings with regard to medication-induced side effects was also not expected. Kohl et al., (1986) found that subjects undergoing motion sickness testing exposed to five different sympathomimetic treatment conditions all experienced significant side effects typically characterized as agitated, jittery, nervous, or uneasy. Wood et al., (1966) and Wood and Graybiel (1968) reported significant side effects when using 10 and 20 mg doses of d-amphetamine with similar subject complaints of agitation and anxiousness. There were no subject complaints of agitation or nervousness during the execution of this study. The results from the KSS confirm the side effect findings, as there were no significant differences in scores of subjective feelings of alertness. These findings may be due to the small dose of d-amphetamine used in this study, although, others have found even small doses to elicit side effects. Alternatively, the present findings may be attributed to the time of day of administration. It is possible that an early arrival (07:15 am), combined with a small dose of stimulant, simply made subjects feel normally awake but the dose was not sufficient to induce anxious feelings.

An assessment of drug-related changes in visual accommodation was conducted during this study and no significant difference in near-focus vision was found between the d-amphetamine

group and the placebo group. This is in contrast to the finding of Wood et al., (1966) who reported a 33% incidence rate of blurred vision, as determined by self-report, with administration of 20 mg d-amphetamine. Subjects in the Wood experiment also reported a fairly high incidence of vertigo in the d-amphetamine condition (22%). If subjects experienced significant dizziness/vertigo while spinning and the symptom questionnaire was collected immediately post-rotation, it is possible that the changes in visual acuity reported in the Wood study were related to vertigo and were not actual drug-related changes in accommodation. The paper by Wood and colleagues lacks the necessary detail in the methods section to determine the proximity of symptom collection to cessation of rotation. The present study allowed sufficient time for the immediate symptoms of rotation to subside before side effect information was collected. The timing was designed to ensure any symptoms collected were medication-related and not a consequence of rotation.

One final area where the data from this experiment deviates from previous d-amphetamine studies is the outcome from the physiological data. Comparison of heart rate and blood pressure data indicate no significant difference in systolic or diastolic blood pressures between groups and only one significantly different time point in heart rate over the 3.5 hour study. Heart rate systematically declined over time in both groups, whereas, blood pressure values remained fairly constant over the course of the experiment. Again, results from previous studies assessing the side effects or physiological effects of d-amphetamine reported different findings. Perez-Reyes, White, McDonald and Hicks (1992) found that .09 and .18 mg/kg of d-amphetamine accelerated heart rate and increased both systolic and diastolic blood pressures. Wood et al., (1966) did not collect physiological data but did report that one subject complained of a headache and a blood pressure reading revealed the pressures had increased from 125/80 mm Hg to 140/90 mm Hg. Any medical physiology textbook (e.g., Guyton, 1991) would indicate an expected increase in heart rate and blood pressures with sympathomimetic compounds. One explanation for these findings is the exposure of subjects to provocative motion. Many studies, and most textbooks, commenting on the physiological action of sympathomimetics are assuming a normal, healthy system not under any extraneous influence. If the parasympathetic nervous system is dominant during inducement of motion sickness, then a temporary decrease in heart rate and blood pressure would be expected. As indicated by figure 7, heart rate in the d-amphetamine group does not begin to increase until 160 minutes post-dose, and systolic and diastolic blood pressure does not follow the small decline seen in the placebo group but remains fairly stable at pre-spin levels. Even though the results were not significant, the data would suggest that d-amphetamine shows the propensity to offset the parasympathetic action of motion sickness and that a larger dose, or perhaps a different sympathomimetic agent, may be effective as a motion sickness countermeasure.

Conclusions and Future Considerations

Although the results from this experiment did not find d-amphetamine to be an effective countermeasure for motion sickness, the concept of using sympathomimetics for motion sickness prophylaxis remains an appealing idea. This study also had several positive outcomes such as, validation of the motion stimulus for future motion sickness work, several important study design concerns, and susceptibility screening recommendations. As our understanding of the cause of motion sickness progresses, future studies should explore new classes of medications, including new sympathomimetics, which may prove more efficacious without inducing

detrimental side effects. In addition, screening for individuals who are susceptible to motion sickness may help reduce the error variance associated with individual differences and allow for more powerful results in motion sickness trials.

Military Significance

Historical research would indicate that select sympathomimetic agents would be ideal anti-motion sickness drugs and well-suited for use in an operational environment. The present study was not able to verify or discount early research suggesting that amphetamine is an efficacious motion sickness countermeasure. With pharmaceutical advances in the area of sympathomimetic and sympathomimetic-like medications, new alternatives within the drug class should be evaluated for anti-motion sickness efficacy rather than a reinvestigation of older medications.

Military assignments require personnel to maintain peak physical and cognitive performance which can be compromised with the wrong medical solutions to operational problems. Of specific importance to military personnel in dynamic environments is the fact that sympathomimetic drugs appear to stimulate speed of neuro-transmission and heighten cognitive awareness while not imparting other performance impairing side effects. With the implementation of Sea Power 21, and the concept of sea-basing in the military's future, motion sickness will become a greater problem, not only for Navy but for Army and Air Force personnel. In addition to the U.S. military, NASA has been seeking a highly effective motion sickness countermeasure without detrimental cognitive and performance side effects. D-amphetamine, for use as both a fatigue countermeasure and anti-motion sickness medication, would be optimal for integration into sea, land, air, and space missions, with the ultimate goal of enhancing the operational effectiveness of military and astronaut populations.

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Disclaimer

The study protocol was approved by the Naval Aerospace Medical Research Laboratory Review Board in compliance with all applicable Federal regulations governing the protection of human subjects.

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Copyright Statement

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Table 1. Descriptive Statistics for D-amphet and Placebo

Group	Sample n	Male/ Female	Mean Age	Weight (kg)	Height (cm)	BMI	MSSQ (Mean, SE)
D-amphet	18	14/4	23.8	82.3	177.5	26.1	4.6 (1.4)
Placebo	18	17/1	23.4	86.3	180.6	26.4	3.6 (1.1)
Total	36	31/5	23.6	84.3	179.1	26.3	4.1 (0.9)

Note. D-amphet = Dextroamphetamine; BMI = Body Mass Index; MSSQ = Motion Sickness Susceptibility Questionnaire-Short Form

Table 2. Estimated Marginal Means for Head Movements using the MSSQ as a Covariate for D-amphet and Placebo

	Mean Head Movements
D-amphet	214± 28.13
Placebo	210± 28.13

Note. MSSQ = Motion Sickness Questionnaire- Short Form, D-amphet = Dextroamphetamine Values are estimated marginal means ± SE.

Table 3. Group Comparisons of Visual Accommodation and Subjective Sleepiness for D-amphet and Placebo.

	Time					
	1	2	3	4	5	6
VA_D	12.24 ± 0.62	12.64 ± 0.65	13.82 ± 0.78	13.82 ± 0.79	13.18 ± 0.63	12.82 ± 0.62
VA_P	11.59 ± 0.50	12.11 ± 0.57	12.71 ± 0.75	12.65 ± 0.87	12.00 ± 0.68	11.59 ± 0.64
KSS_D	4.22 ± 0.38	3.39 ± 0.30	4.50 ± 0.39	3.33 ± 0.32	3.17 ± 0.27	3.22 ± 0.22
KSS_P	3.94 ± 0.42	3.33 ± 0.29	3.44 ± 0.36	3.17 ± 0.35	3.06 ± 0.37	3.50 ± 0.32

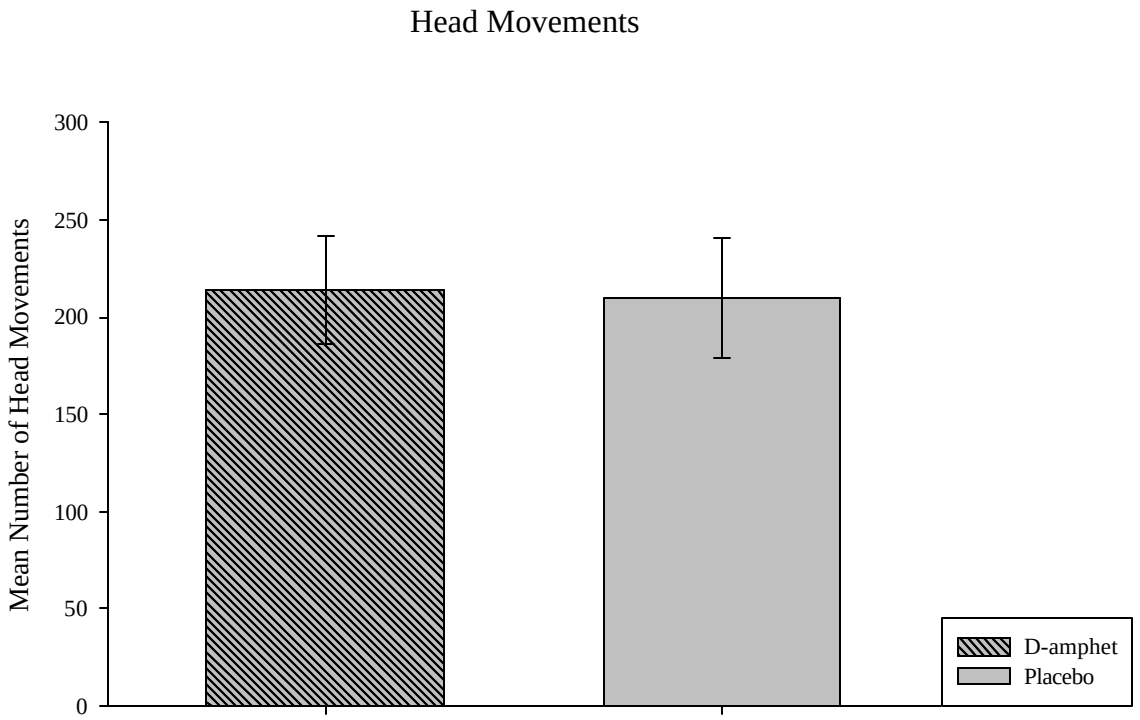
Note. VA = Visual Accommodation (in centimeters) and KSS = Karolinska Sleepiness Scale. D-amphet = Dextroamphetamine. For VA, Times 1-6 correspond with baseline, 55, 115, 140, 165, 185 minutes post-PO dose. Times 1-6 for KSS scores are baseline, 60, 115, 150, 170 & 195 minutes post-PO dose. $_D$ = Dextroamphetamine $_{\& P}$ = Placebo. Values reported as means ± SE.

Table 4. Group Comparisons for the ARES Cognitive Battery for D-amphet and Placebo

	Time				
	1	2	3	4	5
SRT_D	228.89 ± 5.50	226.28 ± 5.77	234.78 ± 6.59	220.11 ± 6.33	223.11 ± 8.40
SRT_P	219.28 ± 6.18	220.56 ± 7.34	223.00 ± 5.65	215.33 ± 5.35	211.33 ± 5.70
RM_D	438.00 ± 14.26	432.50 ± 15.82	432.94 ± 14.53	423.44 ± 13.05	414.33 ± 9.90
RM_P	423.17 ± 16.99	418.44 ± 15.12	411.17 ± 14.22	420.50 ± 14.44	417.94 ± 14.64
MS_D	1102.67 ± 69.19	1086.22 ± 55.38	1226.00 ± 67.15	927.28 ± 41.89	1223.11 ± 89.92
MS_P	886.06 ± 67.57	901.11 ± 51.20	1131.83 ± 88.70	877.44 ± 91.31	897.33 ± 49.49
LR_D	1672.33 ± 115.47	1628.39 ± 113.20	1677.06 ± 137.27	1647.72 ± 116.23	1559.39 ± 119.85
LR_P	1399.50 ± 84.69	1336.00 ± 74.61	1360.94 ± 85.87	1402.67 ± 74.19	1378.44 ± 71.80

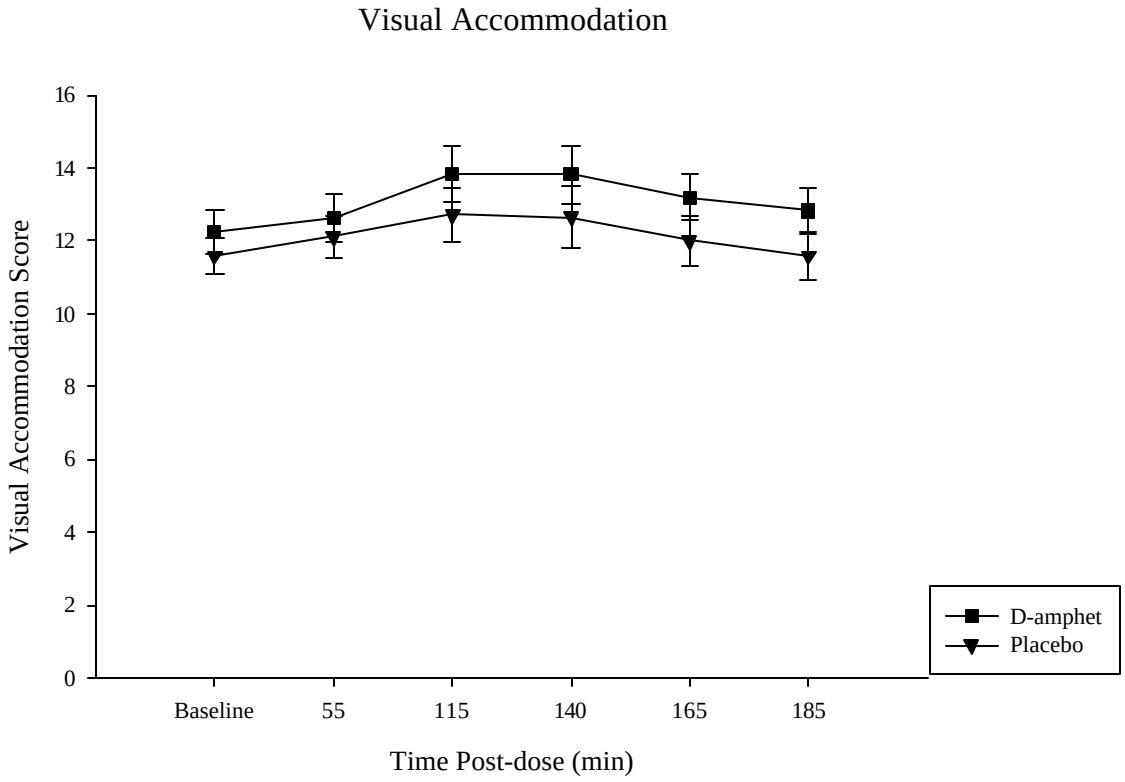
Note: All scores in milliseconds. SRT = Simple Reaction Time, RM = Running Memory, MS = Matching to Sample, LR= Logical Reasoning. $_D$ = Dextroamphetamine $_{\& P}$ = Placebo. Times 1-5 correspond with Baseline and 55, 140, 165, & 185 minutes post-PO SCOP dose, respectively. All values are reported as means ± SE.

Figure 1. Average Number of Head Movements to Moderate Nausea for D-amphet and Placebo



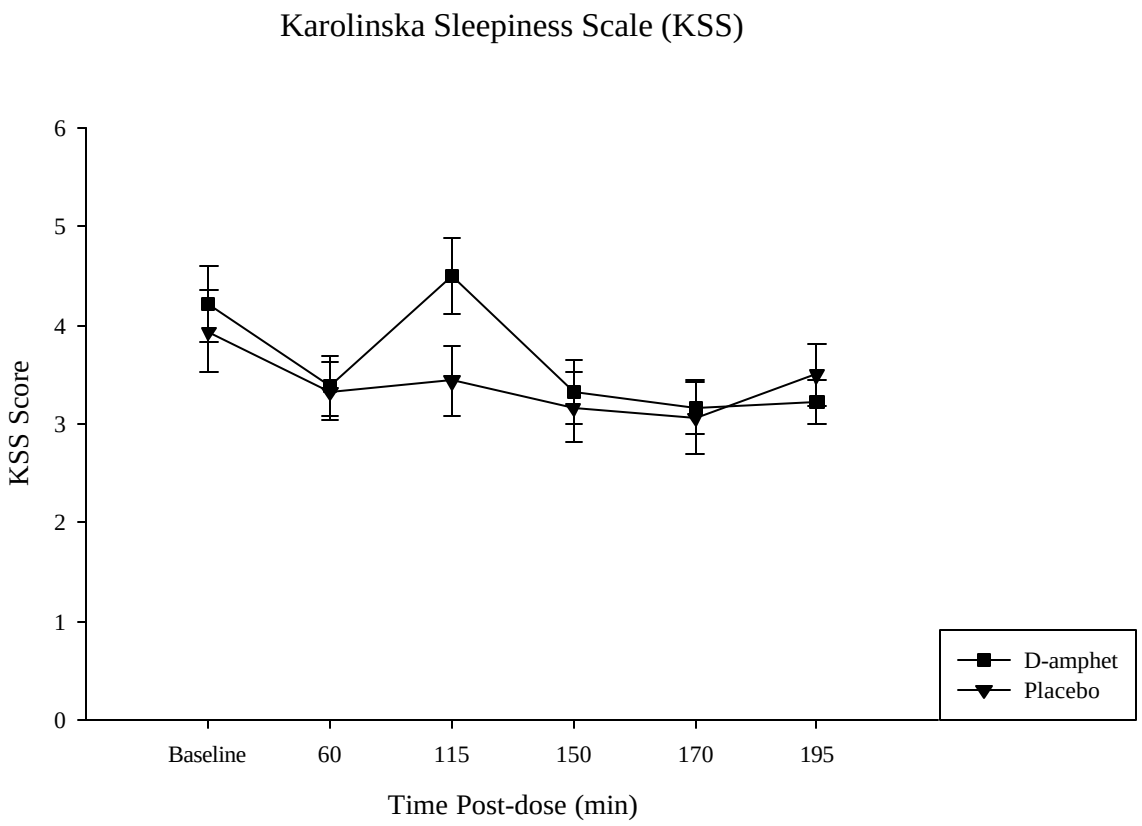
Note. D-amphet = Dextroamphetamine. No significant difference in number of head movements tolerated between the D-amphet and placebo groups (p>0.05). Values are reported as estimated marginal means ± SE.

Figure 2. Visual Accommodation Scores Over Six Observations for D-amphet and Placebo



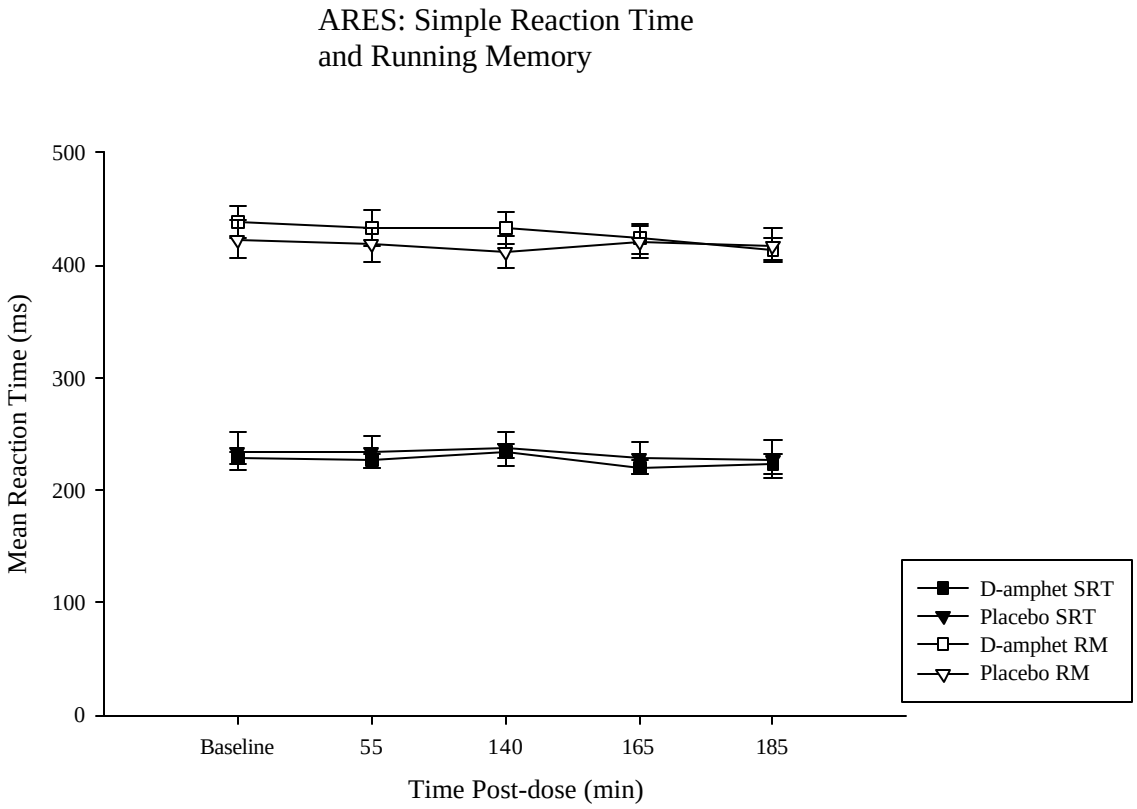
Note. D-amphet = Dextroamphetamine. No significant difference in visual accommodation scores over time between the D-amphet and placebo groups (p>0.05). All values are reported as means ± SE.

Figure 3. Karolinska Sleepiness Scale scores over six observations for D-amphet and Placebo



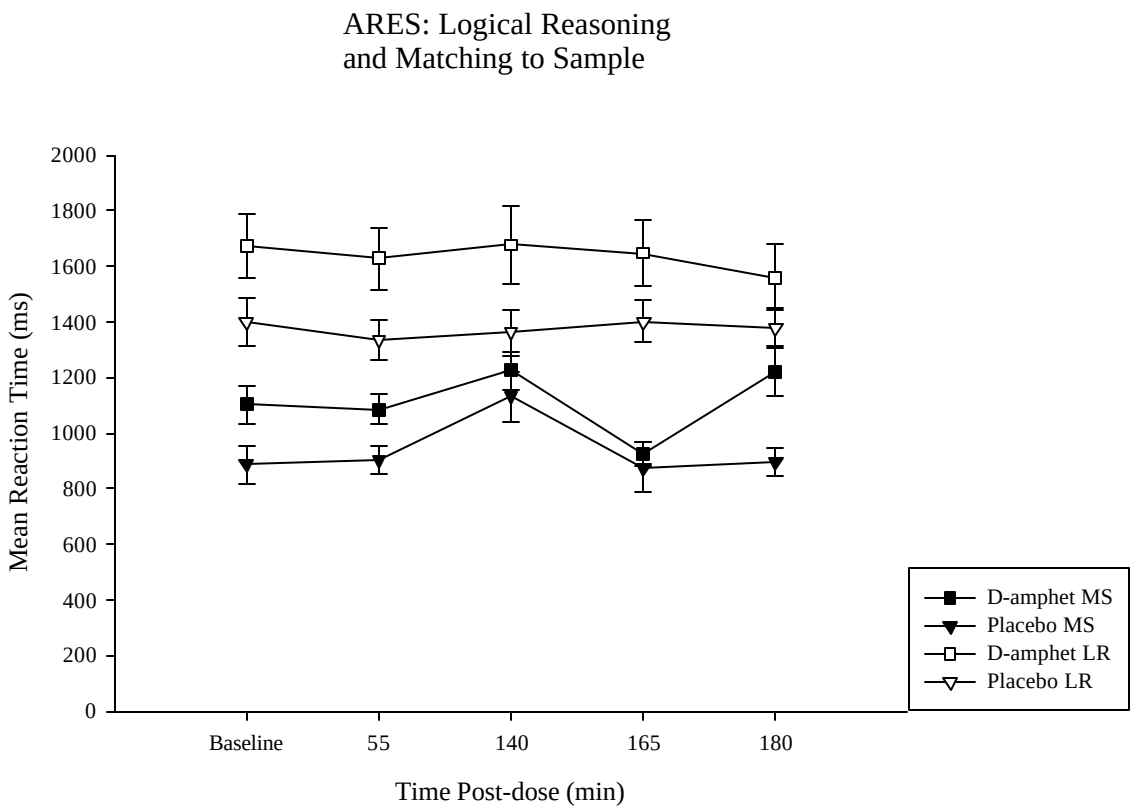
Note. D-amphet = Dextroamphetamine. No significant difference in KSS scores over time between the D-amphet and placebo groups (p>0.05). All values are reported as means ± SE.

Figure 4. ARES Results for Simple Reaction Time and Running Memory Over Five Time Points for D-amphet and Placebo



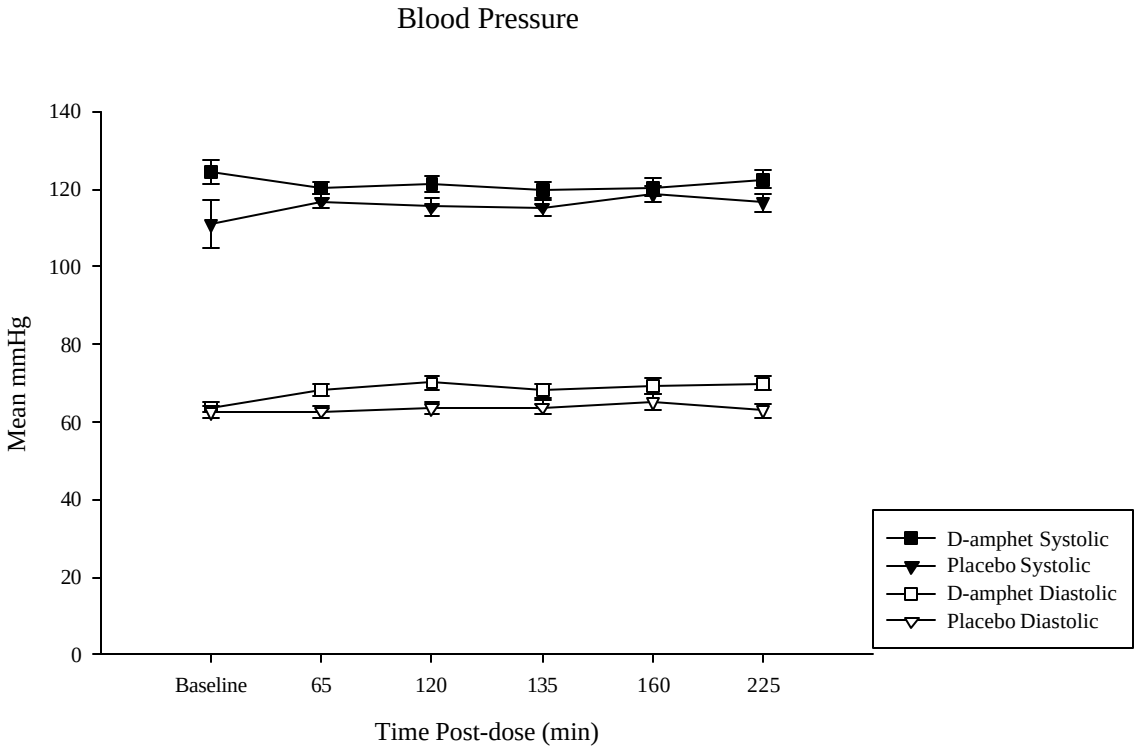
Note. D-amphet = Dextroamphetamine. No significant drug by time interaction for ARES SRT and RM scores between D-amphet and placebo groups (p>0.05). All values are reported as means ± SE.

Figure 5. ARES Results for Logical Reasoning and Matching to Sample Over Five Time Points for D-amphet and Placebo



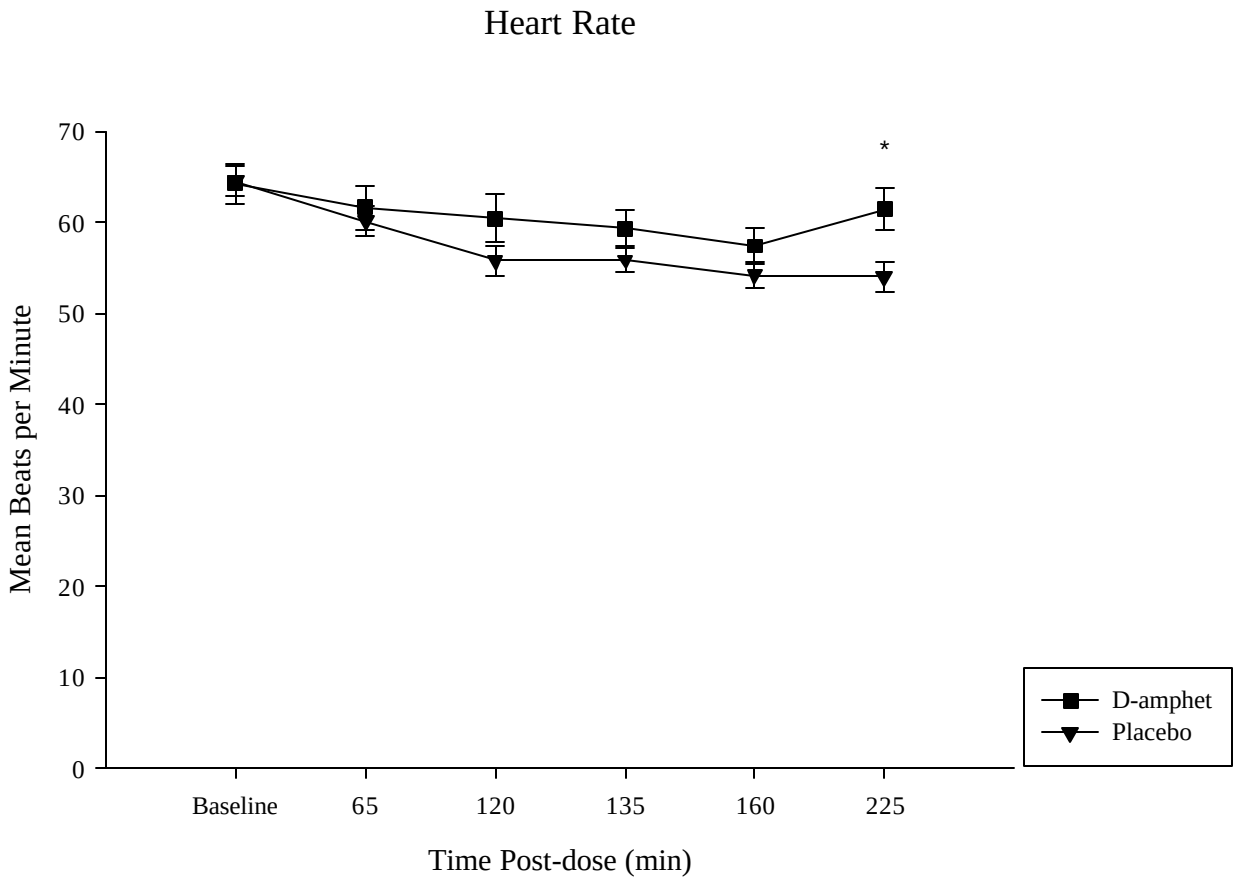
Note. D-amphet = Dextroamphetamine. No significant drug by time interaction for ARES LR and MTS scores between D-amphet and placebo groups ($p>0.05$). All values are reported as means ± SE.

Figure 6. Change in Blood Pressure Over Six Time Points for D-amphet and Placebo



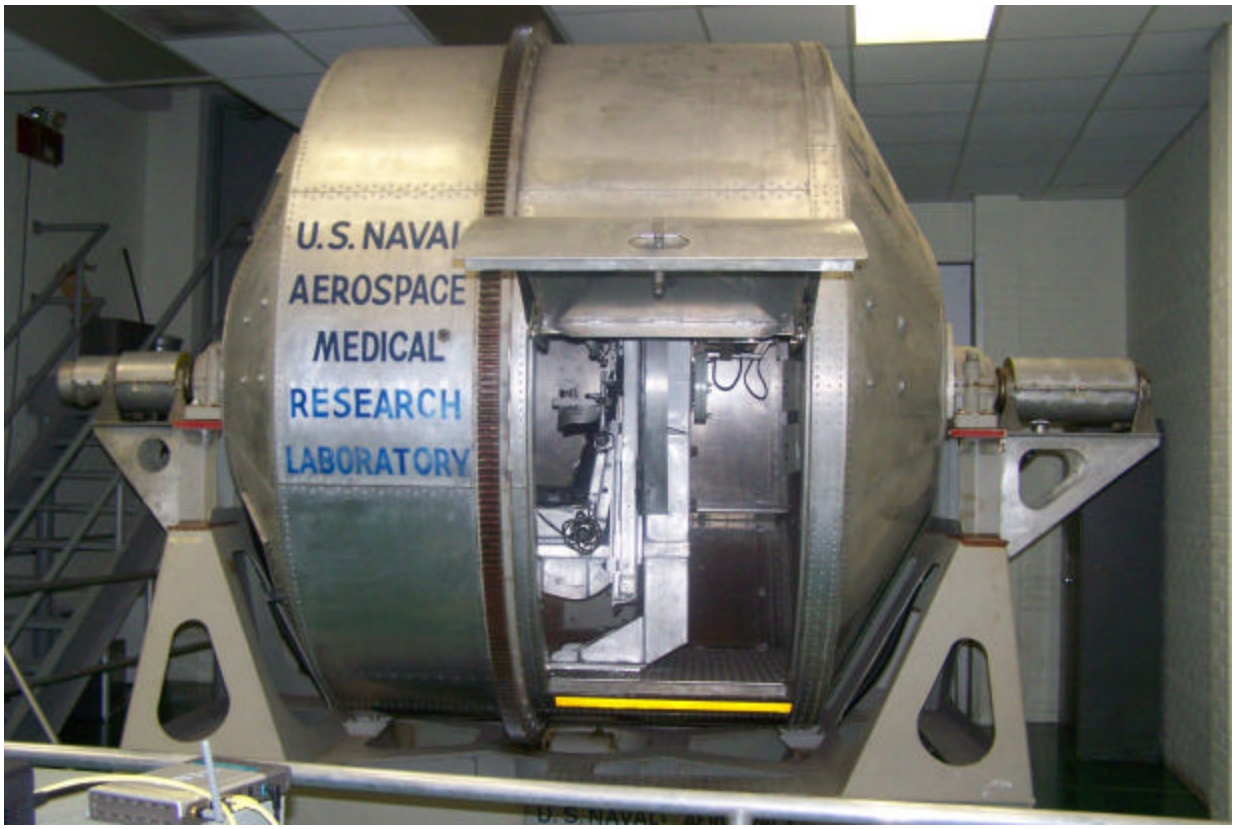
Note. D-amphet = Dextroamphetamine. No significant difference in systolic or diastolic blood pressures over time between D-amphet and placebo groups (p>0.05). All values are reported as means ± SE.

Figure 7. Change in Heart Rate Over Six Time Points for D-amphet and Placebo



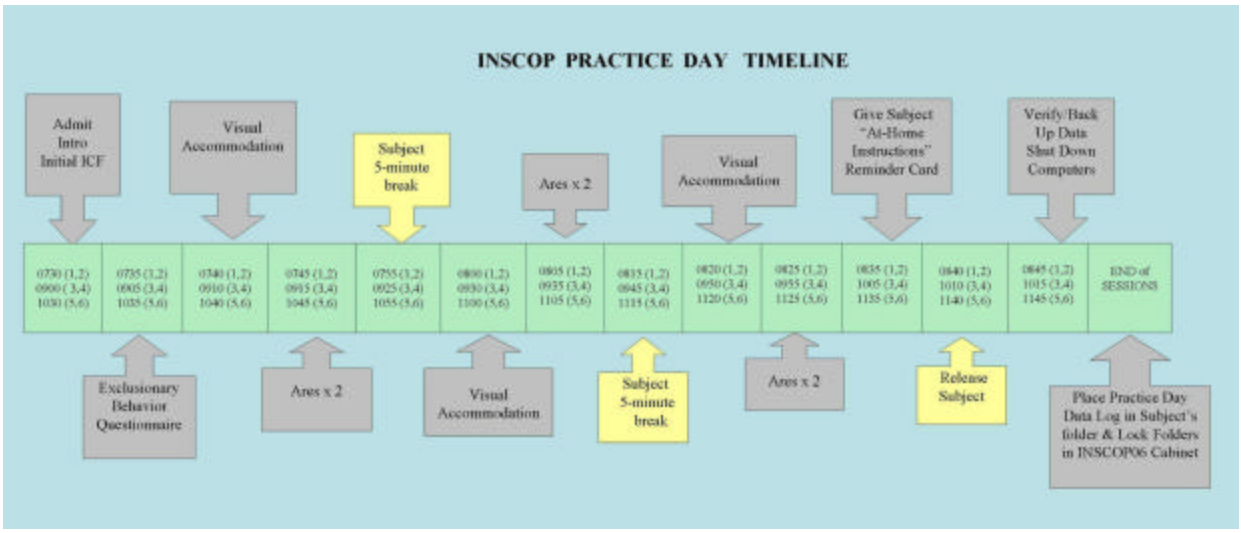
Note. D-amphet = Dextroamphetamine; Significant difference between D-amphet and Placebo 225 minutes post-dose (*), $p<0.05$. All values are reported as means ± SE.

Appendix 1. Picture of Human Disorientation Device

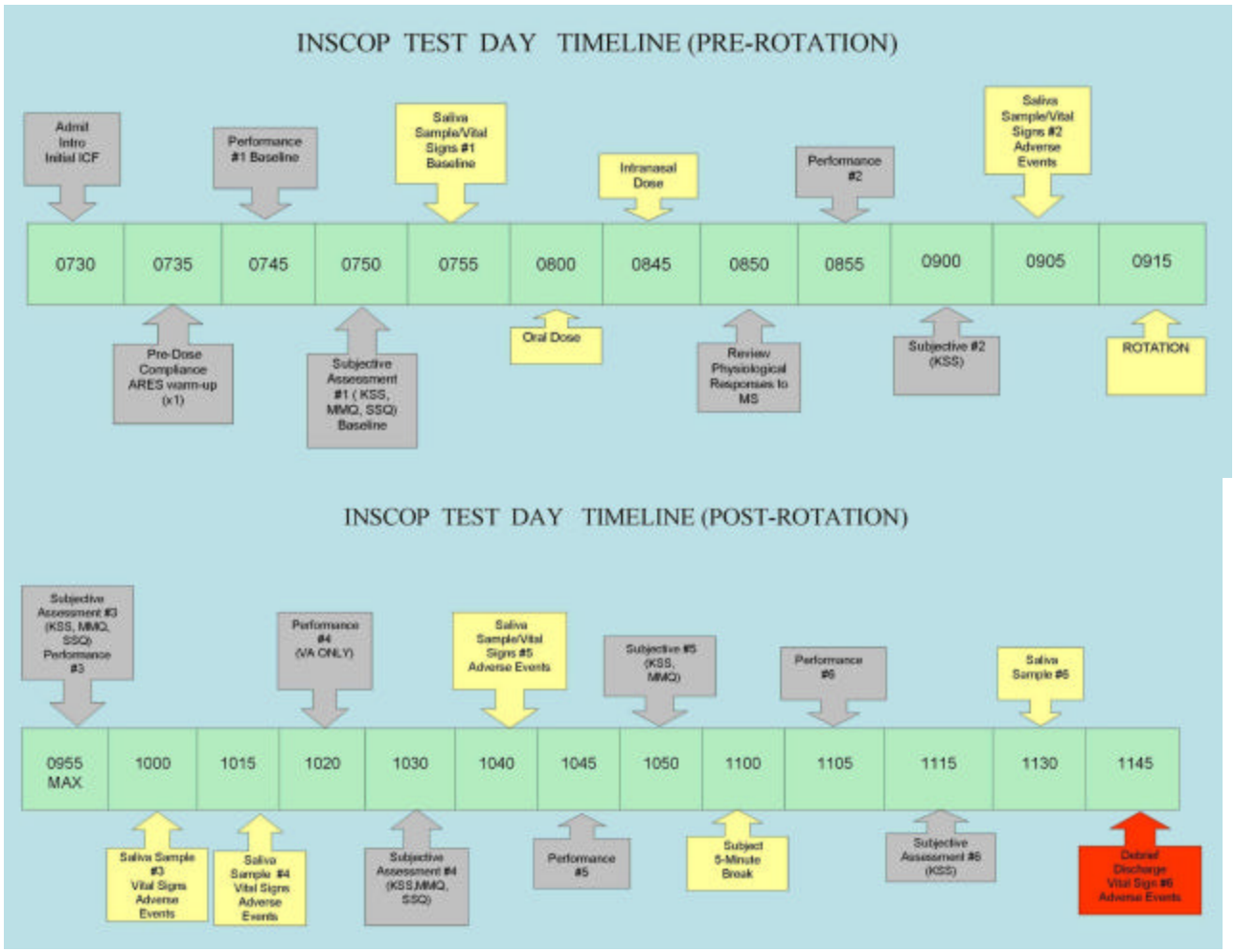


Appendix 2. RAF Rule

Appendix 3. Practice Day Timeline



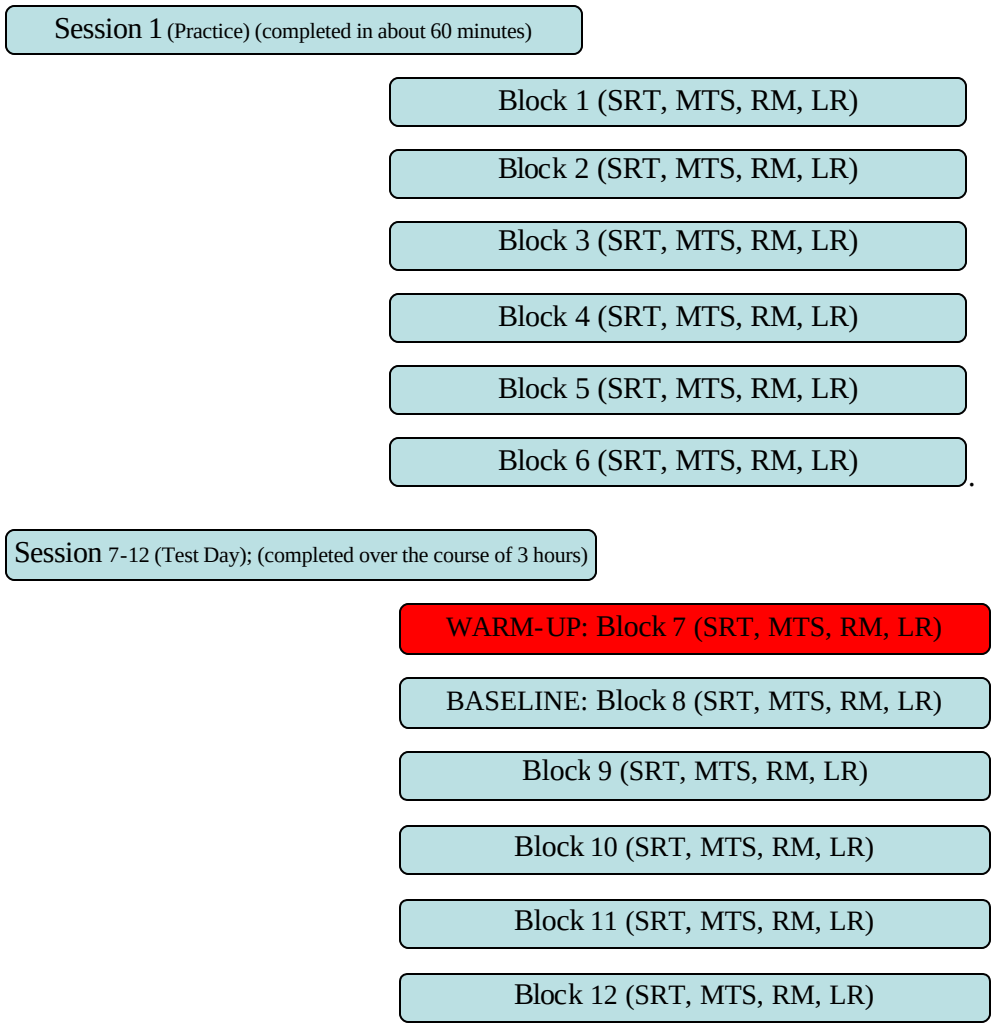
Appendix 4. Test Day Timeline



Appendix 5. ARES Administration

I. Description of the Administration of the ARES Cognitive Battery

There were 2 testing sessions of the ARES Cognitive Battery for each subject. Both sessions contained 6 blocks of testing.



Each Block consists of 4 tests (given in the same order each session):

Simple Reaction Time - number of stimuli and time varied, and involved 15-20 stimuli (*) for approximately 30-40 seconds.

Matching To Sample - involved 10 stimuli (varied sequence) and lasted approximately 100-115 seconds (depending on reaction time).

Running Memory - generally has 80 stimuli (varied sequence), unless the reactions times were "slow", and then it decreased to 78 or 79. Times ranges from 130 to 160 seconds.

Logical Reasoning - involved 24 stimuli (varied sequence) and lasted approximately 60 to 90 seconds.

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13. SUPPLEMENTARY NOTES

14. ABSTRACT Previous research examining pharmacological solutions for motion sickness have reported that dextroamphetamine (d-amphetamine) imparts significant protection against provocative motion without conferring drowsiness or significant side effects. If the purported anti-motion sicknesses properties of d-amphetamine are accurate, the military could utilize a single medication for motion sickness and fatigue prevention. The purpose of this study was to determine the efficacy and side effect profile of this potential motion sickness countermeasure for use in military environments. It was hypothesized that subjects in the oral d-amphetamine condition would tolerate more head movements than subjects in the placebo condition, without performance decrements or significant side effects. Thirty-six aviation candidates were randomized to one of two treatment groups and then exposed to passive Coriolis cross-coupling. Medication efficacy was determined by number of head movements tolerated between groups. Cognitive and medication side-effect profiles for both groups were derived from performance on a computer based cognitive battery, measurements of near-focus visual accommodation (VA), scores on the Karolinska Sleepiness Scale (KSS), and motion sickness questionnaires. Analyses demonstrated that there were no significant differences in the number of head movements tolerated between groups and no treatment effects over time on the cognitive battery, VA, or KSS, $p > 0.05$.

15. SUBJECT TERMS

motion sickness, motion sickness countermeasures, dextroamphetamine, stimulants, effects of dextroamphetamine on cognition

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